Amendment

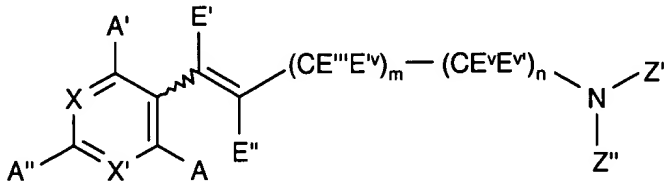
In the Specification:

At page 2, lines 8-21, please delete the present paragraph and insert the following:

The present invention relates to aryl substituted olefinic amine compounds. Representative compounds are (4E)-N-methyl-5-(3-pyridyl)-4-penten-2-amine, (4E)-N-methyl-5-(5-pyrimidinyl)-4-penten-2-amine, (4E)-N-methyl-5-(5-methoxy-3-pyridyl)-4-penten-2-amine, (4E)-N-methyl-5-(6-amino-5-methyl-3-pyridyl)-4-penten-2-amine, (2R)-(4E)-N-methyl-5-(3-pyridyl)-4-penten-2-amine, (2R)-(4E)-N-methyl-5-(5-isopropoxy-3-pyridyl)-4-penten-2-amine, (4E)-N-methyl-5-(5-bromo-3-pyridyl)-4-penten-2-amine, (4E)-N-methyl-5-(5-ethoxy-3-pyridyl)-4-penten-2-amine, (2S)-(4E)-N-methyl-5-(3-pyridyl)-4-penten-2-amine, (4E)-N-methyl-5-(5-isopropoxy-3-pyridyl)-4-penten-2-amine and (2S)-(4E)-N-methyl-5-(5-isopropoxy-3-pyridyl)-4-penten-2-amine. The present invention also relates to methods for synthesizing certain aryl substituted olefinic amine compounds, such as the compounds of the present invention. Of particular interest are isolated ~~enamiomeric~~ enantiomeric compounds (i.e., compounds in a substantially pure form, as opposed to racemic mixtures), and methods for synthesizing such ~~enamiomeric~~ enantiomeric compounds in substantially pure form.

At page 5, line 1 through page 7, line 5, please delete the present paragraph and insert the following:

The compounds of the present invention include compounds of the formula:



where each of X and X' are individually nitrogen or carbon bonded to a substituent species characterized as having a sigma m value greater than 0, often greater than 0.1, and generally greater than 0.2, and even greater than 0.3; less than 0 and generally less than -0.1; or 0; as

determined in accordance with Hansch et al., *Chem. Rev.* **91**:165 (1991); m is an integer and n is an integer such that the sum of m plus n is 1, 2, 3, 4, 5, 6, 7, or 8, preferably is 1, 2, or 3, and most preferably is 2 or 3; the wavy line in the structure indicates that the compound can have the cis (Z) or trans (E) form; E^{I}, E^{II}, E^{III}, E^{IV}, E^{V} and E^{VI} individually represent hydrogen or lower alkyl (e.g., straight chain or branched alkyl including C_1-C_8, preferably C_1-C_5, such as methyl, ethyl, or isopropyl) or halo substituted lower alkyl (e.g., straight chain or branched alkyl including C_1-C_8, preferably C_1-C_5, such as trifluoromethyl or trichloromethyl), and at least one of E^{I}, E^{II}, E^{III}, E^{IV}, E^{V} and E^{VI} is non-hydrogen and the remaining E^{I}, E^{II}, E^{III}, E^{IV}, E^{V} and E^{VI} are hydrogen; and Z′ and Z″ individually represent hydrogen or lower alkyl (e.g., straight chain or branched alkyl including C_1-C_8, preferably C_1-C_5, such as methyl, ethyl, or isopropyl), and preferably at least one of Z′ and Z″ is hydrogen, and most preferably Z′ is hydrogen and Z″ is methyl; alternatively Z′ is hydrogen and Z″ represents a ring structure (cycloalkyl or aromatic), such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, quinuclidinyl, pyridyl, quinolinyl, pyrimidinyl, phenyl, benzyl (where any of the foregoing can be suitably ~~substiuted~~ substituted with at least one substituent group, such as alkyl, halo, or amino substituents); alternatively Z′, Z″, and the associated nitrogen atom can form a ring structure such as aziridinyl, azetidinyl, pyrollidinyl, piperidinyl, quinuclidinyl, piperazinyl, or morpholinyl. More specifically, X and X' include N, C-H, C-F, C-Cl, C-Br, C-I, C-R′, C-NR′R″, C-CF_3, C-OH, C-CN, C-NO_2, C-C_2R′, C-SH, C-SCH_3, C-N_3, C-SO_2CH_3, C-OR′, C-SR′, C-C(=O)NR′R″, C-NR′C(=O)R′, C-C(=O)R′, C-C(=O)OR′, $C(CH_2)_q$OR′, C-OC(=O)R′, COC(=O)NR′R″ and C-NR′C(=O)OR′ where R′ and R″ are individually hydrogen or lower alkyl (e.g., C_1-C_{10} alkyl, preferably C_1-C_5 alkyl, and more preferably methyl, ethyl, isopropyl or isobutyl), an aromatic group-containing species or a substituted aromatic group-containing species, and q is an integer from 1 to 6. R′ and R″ can be straight chain or branched alkyl, or R′ and R″ can form a cycloalkyl ~~funtionality~~ functionality (e.g., cyclopropyl cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, and quinuclidinyl). Representative aromatic group-containing species include pyridyl, quinolinyl, pyrimidinyl, phenyl, and benzyl (where any of the foregoing can be suitably substituted with at least one substituent group, such as alkyl, halo, or amino substituents). Other representative aromatic ring systems are set forth in Gibson et al., *J. Med. Chem.* **39**:4065 (1996). When X and X' represent a carbon atom bonded to a substituent species, that substituent species often has a sigma m value which is between about -0.3 and about 0.75, and frequently between about -0.25 and about 0.6. In certain circumstances

the substituent species is characterized as having a sigma m value not equal to 0. A, A′ and A″ individually represent those species described as substituent species to the aromatic carbon atom previously described for X and X'; and usually include hydrogen, halo (e.g., F, Cl, Br, or I), alkyl (e.g., lower straight chain or branched C_{1-8} alkyl, but preferably methyl or ethyl), or NX''X''' where X'' and X''' are individually hydrogen or lower alkyl, including C_1-C_8, preferably C_1-C_5 alkyl. In addition, it is highly preferred that A is hydrogen, it is preferred that A′ is hydrogen, and normally A″ is hydrogen. Generally, both A and A′ are hydrogen; sometimes A and A′ are hydrogen, and A″ is amino, methyl or ethyl; and often A, A′ and A″ are all hydrogen. In a preferred embodiment, m is 1 or 2, n is 1, E^I, E^{II}, E^{III}, E^{IV} and E^{VI} each are hydrogen, and E^V is alkyl (e.g., methyl). Depending upon the identity and positioning of each individual E^I, E^{II}, E^{III}, E^{IV}, E^V and E^{VI}, certain compounds can be optically active. Additionally, compounds of the present invention can have chiral centers within the alkenyl side chain e.g., the compound can have an R or S configuration depending on the selection of E^{III}, E^{IV}, E^V and E^{VI}, with the S configuration being preferred. Depending upon E^I, E^{II}, E^{III}, E^{IV}, E^V and E^{VI}, compounds of the present invention have chiral centers, and the present invention relates to racemic mixtures of such compounds as well as ~~enamiomeric~~ enantiomeric compounds. Typically, the selection of m, n, E^I, E^{II}, E^{III}, E^{IV}, E^V and E^{VI} is such that up to about 4, and frequently up to 3, and usually 1 or 2, of the substituents designated as E^I, E^{II}, E^{III}, E^{IV}, E^V and E^{VI} are non-hydrogen substituents (i.e., substituents such as lower alkyl or halo-substituted lower alkyl). Typically, X is CH, CBr or COR. Most preferably, X' is nitrogen.

At page 9, line 21 through page 10, line 12, please delete the present paragraph and insert the following:

There are a number of methods by which the (Z)-olefinic isomers of aryl substituted olefinic amine compounds can be synthetically produced. In one approach, the (Z)-isomers of aryl substituted olefinic amine compounds can be prepared by the controlled hydrogenation of the corresponding alkynyl compounds (e.g., a N-methyl-5-(3-pyridyl)-4-butyn-2-amine-type compound) using commercially available Lindlar catalyst (Aldrich Chemical Company) using the methodology set forth in H. Lindlar et al., *Org. Syn.* **46**: 89 (1966). The requisite alkynyl compounds can be prepared by the palladium catalyzed coupling of an aromatic halide, preferably a 3-bromopyridine-type or a 3-iodopyridine-type compound with an alkynyl side

chain compound (e.g., an N-methyl-4-pentyn-2-amine-type compound). Typically, the ~~methodolgy~~ methodology set forth in L. Bleicher et al., *Synlett.* 1115 (1995) is used for the palladium catalyzed coupling of an aryl halide with a monosubstituted alkyne in the presence of copper(I) iodide and triphenylphosphine and potassium carbonate as a base. Alkynyl compounds such as N-methyl-4-pentyn-2-amine can be prepared from commercially available 4-pentyn-2-ol (Aldrich Chemical Company) by treatment with p-toluenesulfonyl chloride in pyridine, followed by reaction of the resulting 4-pentyn-2-ol p-toluenesulfonate with excess methylamine either as a 40% aqueous solution or as a 2.0 M solution in tetrahydrofuran. In some instances it may be necessary to protect the amino functionality of the N-methyl-4-pentyn-2-amine-type compound by treatment with di-tert-butyl dicarbonate to give the tert-butoxycarbonyl protected amine-type compound. Such protected amine compounds may undergo the palladium catalyzed coupling with aryl halides and the subsequent controlled hydrogenation of the resulting alkynyl compound more easily than the unprotected amine compounds. The tert-butoxycarbonyl protecting group can be easily removed using a strong acid such as trifluoroacetic acid to yield the (Z)-olefinic isomers of aryl substituted olefinic amine compounds.

At page 11, line 20 through page 12, line 28, please delete the present paragraph and insert the following:

The manner in which certain aryl substituted olefinic amine compounds possessing a branched side chain, such as (4E)-N-methyl-5-(5-isopropoxy-3-pyridyl)-4-penten-2-amine, are provided can vary. By using one synthetic approach, the latter compound can be synthesized in a convergent manner, in which the side chain, N-methyl-N-(tert-butoxycarbonyl)-4-penten-2-amine is coupled with the 3-substituted 5-halo-substituted pyridine, 5-bromo-3-isopropoxypyridine, under Heck reaction conditions, followed by removal of the tert-butoxycarbonyl protecting group. Typically, the types of procedures set forth in W. C. Frank et al., *J. Org. Chem.* **43**: 2947 (1978) and N. J. Malek et al., *J. Org. Chem.* **47**: 5395 (1982) involving a palladium-catalyzed coupling of an olefin and an aromatic halide are used. The required N-methyl-N-(tert-butoxycarbonyl)-4-penten-2-amine can be synthesized as follows: (i) ~~Commercially~~ commercially available 4-penten-2-ol (Aldrich Chemical Company, Lancaster Synthesis Inc.) can be treated with p-toluenesulfonyl chloride in pyridine to yield 4-penten-2-ol p-toluenesulfonate, previously described by T. Michel, et al., *Liebigs Ann.* **11**: 1811 ~~(1996).~~

(1996); (ii) ~~The~~ the resulting tosylate can be heated with 20 molar equivalents of methylamine as a 40% aqueous solution to yield ~~N-methyl-4-penten-2-amine.~~ N-methyl-4-penten-2-amine; and (iii) ~~The~~ the resulting amine, such as previously mentioned by A. Viola et al., *J. Chem. Soc., Chem. Commun.* **(21)**: 1429 (1984), can be allowed to react with 1.2 molar equivalents of di-tert-butyl dicarbonate in dry tetrahydrofuran to yield the side chain, N-methyl-N-(tert-butoxycarbonyl)-4-penten-2-amine. The halo-substituted pyridine, (e.g., 5-bromo-3-isopropoxypyridine) can be synthesized by two different routes. In one preparation, 3,5-dibromopyridine is heated at 140°C for 14 hours with 2 molar equivalents of potassium isopropoxide in dry isopropanol in the presence of copper powder (5%, w/w of the 3,5-dibromopyridine) in a sealed glass tube to yield 5-bromo-3-isopropoxypyridine. A second preparation of 5-bromo-3-isopropoxypyridine from 5-bromonicotinic acid can be performed as follows: (i) 5-Bromonicotinic acid is converted to 5-bromonicotinamide by treatment with thionyl chloride, followed by reaction of the intermediate acid chloride with aqueous ~~ammonia.~~ ammonia; (ii) ~~The~~ the resulting 5-bromonicotinamide, previously described by C. V. Greco et al., *J. Heteocyclic Chem.* **7(4)**: 761 (1970), is subjected to Hofmann degradation by treatment with sodium hydroxide and a 70% solution of calcium ~~hypochlorite.~~ hypochlorite; and (iii) ~~The~~ the resulting 3-amino-5-bromopyridine, previously described by C. V. Greco et al., *J. Heteocyclic Chem.* **7(4)**: 761 (1970), can be converted to 5-bromo-3-isopropoxypyridine by diazotization with isoamyl nitrite under acidic conditions, followed by treatment of the intermediate diazonium salt with isopropanol to yield 5-bromo-3-isopropoxypyridine. The palladium-catalyzed coupling of 5-bromo-3-isopropoxypyridine and N-methyl-N-(tert-butoxycarbonyl)-4-penten-2-amine is carried out in acetonitrile-triethylamine (2:1, v,v) using a catalyst consisting of 1 mole % palladium(II) acetate and 4 mole % tri-o-tolylphosphine. The reaction can be carried out by heating the components at 80°C for 20 hours to yield (4E)-N-methyl-N-(tert-butoxycarbonyl)-5-(5-isopropoxy-3-pyridyl)-4-penten-2-amine. Removal of the tert-butoxycarbonyl protecting group can be accomplished by treatment with 30 molar equivalents of trifluoroacetic acid in anisole at 0°C to afford (4E)-N-methyl-5-(5-isopropoxy-3-pyridyl)-4-penten-2-amine.

At page 14, line 25 through page 15, line 16, please delete the present paragraph and insert the following:

The present invention relates to a method for providing prevention of a condition or disorder to a subject susceptible to such a condition or disorder, and for providing treatment to a subject suffering therefrom. For example, the method comprises administering to a patient an amount of a compound effective for providing some degree of prevention of the progression of a CNS disorder (i.e., provide protective effects), amelioration of the symptoms of a CNS disorder, and amelioration of the recurrence of a CNS disorder. The method involves administering an effective amount of a compound selected from the general formulae which are set forth hereinbefore. The present invention relates to a pharmaceutical composition incorporating a compound selected from the general formulae which are set forth hereinbefore. Optically active compounds can be employed as racemic mixtures or as enantiomers. The compounds can be employed in a free base form or in a salt form (e.g., as pharmaceutically acceptable salts). Examples of suitable pharmaceutically acceptable salts include inorganic acid addition salts such as hydrochloride, hydrobromide, sulfate, phosphate, and nitrate; organic acid addition salts such as acetate, galactarate, propionate, succinate, lactate, glycolate, malate, tartrate, citrate, maleate, fumarate, methanesulfonate, p-toluenesulfonate, and ascorbate; salts with acidic amino ~~acid~~ acids such as aspartate and glutamate; alkali metal salts such as sodium salt and potassium salt; alkaline earth metal salts such as magnesium salt and calcium salt; ammonium salt; organic basic salts such as trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, and N,N'-dibenzylethylenediamine salt; and salts with basic amino ~~acid~~ acids such as lysine salt and arginine salt. The salts may be in some cases hydrates or ethanol solvates. Representative salts are provided as described in U.S. Patent Nos. 5,597,919 to Dull et al., 5,616,716 to Dull et al. and 5,663,356 to Ruecroft et al.

At page 20, line 21 through page 21, line 2, please delete the present paragraph and insert the following:

Compounds of the present invention, when employed in effective amounts in accordance with the method of the present invention, are effective towards providing some degree of prevention of the progression of CNS disorders, amelioration of the symptoms of CNS disorders, and amelioration to some degree of the recurrence of CNS disorders. However, such effective amounts of those compounds are not sufficient to elicit any appreciable side effects, as is demonstrated by decreased effects on preparations believed to reflect effects on the

cardiovascular system, or effects to skeletal muscle. As such, administration of compounds of the present invention provides a therapeutic window in which treatment of certain CNS disorders is provided, and side effects are avoided. That is, an effective dose of a compound of the present invention is sufficient to provide the desired effects upon the CNS, but is insufficient (i.e., is not at a high enough level) to provide undesirable side effects. Preferably, effective administration of a compound of the present invention resulting in treatment of CNS disorders occurs upon administration of less than 1/3, frequently less than 1/5, and often less than 1/10, that amount sufficient to cause any side effects to a significant degree.

At page 23, lines 10-16, please delete the present paragraph and insert the following:

A mixture of 3-bromopyridine (7.50 g, 47.46 mmol), 4-penten-2-ol (4.90 g, 56.96 mmol), palladium(II) acetate (106 mg, 0.47 mmol), tri-o-tolylphosphine (575 mg, 1.89 mmol), triethylamine (28.4 mL, 204.11 mmol) and acetonitrile (25 mL) ~~were~~ was heated in a sealed glass tube at 140°C for 14 h. The reaction mixture was cooled to ambient temperature, diluted with water, and extracted with chloroform (3 x 200 mL). The combined chloroform extracts were dried over sodium sulfate, filtered, and concentrated by rotary evaporation to give a pale-yellow oil (7.50 g, 81.0 %).

At page 25, line 30 through page 26, line 7, please delete the present paragraph and insert the following:

A mixture of 3-bromopyridine (11.22 g, 70.58 mmol), (2S)-4-penten-2-ol (5.00 g, 58.05 mmol), palladium(II) acetate (527 mg, 2.35 mmol), tri-o-tolylphosphine (1.79 g, 5.88 mmol), triethylamine (30 mL, 216 mmol) and acetonitrile (30mL) ~~were~~ was heated in a sealed glass tube at 130-140°C for 8 h. The reaction mixture was cooled to ambient temperature. The solvent was removed under reduced pressure on a rotary evaporator. Water (20 mL) was added and the mixture was extracted with chloroform (4 x 50 mL). The combined chloroform extracts were dried (K_2CO_3), filtered, and concentrated by rotary evaporation, producing a pale-yellow oil (6.00 g). The crude product was purified by column chromatography over silica gel, eluting with chloroform-acetone (95:5, v/v). Selected fractions were combined and concentrated by rotary evaporation, affording 3.95 g (41.7%) of a pale-yellow oil.

At page 27, line 31-32, please delete the present paragraph and insert the following:

Sample No. is 3 (2S)-(4E)-N-methyl-5-(3-pyridyl)-4-penten-2-amine hemigalactarate, which was prepared in accordance with the following techniques:

At page 28, lines 9-15, please delete the present paragraph and insert the following:

A mixture of 3-bromopyridine (9.17 g, 58.04 mmol), (2R)-4-penten-2-ol (6.00 g, 69.65 mmol), palladium(II) acetate (130 mg, 0.58 mmol), tri-o-tolylphosphine (710 mg, 2.32 mmol), triethylamine (34.7 mL, 249.5 mmol), and acetonitrile (35 mL) ~~were~~ was heated in a sealed glass tube at 140°C for 14 h. The reaction mixture was cooled to ambient temperature, diluted with water, and extracted with chloroform (3 x 200 mL). The combined chloroform extracts were dried over sodium sulfate, filtered, and concentrated by rotary evaporation to give 6.17 g (65.2%) of a pale-yellow oil.

At page 33, lines 22-32, please delete the present paragraph and insert the following:

Under a nitrogen atmosphere, a mixture of 5-bromo-3-isopropoxypyridine (847.0 mg, 3.92 mmol), N-methyl-N-(tert-butoxycarbonyl)-4-penten-2-amine (784.7 mg, 3.94 mmol), palladium(II) acetate (9.0 mg, 0.04 mmol), tri-o-tolylphosphine (50.0 mg, 0.16 mmol), triethylamine (0.73 g, 7.21 mmol), and anhydrous acetonitrile (2 mL) was stirred and heated under reflux at 80°C for 20 h. The ~~mixture, containing~~ mixture containing solids was cooled, diluted with water (10 mL), and extracted with $CHCl_3$ (3 x 10 mL). The combined $CHCl_3$ extracts were dried (Na_2SO_4), filtered, and concentrated by rotary evaporation to give an oily residue (1.56 g). The crude product was purified by column chromatography on silica gel, eluting with 25→40% (v/v) ethyl acetate in hexane. Selected fractions containing the product were combined and concentrated to give 1.15 g (87.8%) of a light-amber oil.

At page 36, lines 18-28, please delete the present paragraph and insert the following:

A mixture of 5-bromo-3-isopropoxypyridine (12.56 g, 58.13 mmol), (2S)-4-penten-2-ol (5.00 g, 58.05 mmol), palladium(II) acetate (130 mg, 0.58 mmol), tri-o-tolylphosphine (706 mg, 2.32 mmol), triethylamine (35 mL, 252 mmol) and acetonitrile (35mL) ~~were~~ was heated in a sealed glass tube at 130-140°C for 8 h. The reaction mixture was cooled to ambient temperature. The solvent was removed under reduced pressure on a rotary evaporator. Water (50 mL) was added and the mixture was extracted with chloroform (3 x 50 mL). The combined chloroform extracts were dried (K_2CO_3), filtered, and concentrated by rotary evaporation. The crude product was purified by column chromatography over silica gel, eluting with chloroform-acetone (95:5, v/v). Selected fractions were combined and concentrated by rotary evaporation, producing 7.80 g (60.7%) of a pale-yellow oil.

At page 39, lines 1-8, please delete the present paragraph and insert the following:

A mixture of 5-bromo-3-isopropoxypyridine (10.26 g, 47.50 mmol), (2R)-4-penten-2-ol (4.91 g, 57.00 mmol), palladium(II) acetate (106 mg, 0.47 mmol), tri-o-tolylphosphine (578 mg, 1.90 mmol), triethylamine (28.46 mL, 204.25 mmol), and acetonitrile (30 mL) ~~were~~ was heated in a sealed glass tube at 140°C for 14 h. The reaction mixture was cooled to ambient temperature, diluted with water, and extracted with chloroform (3 x 200 mL). The combined chloroform extracts were dried over sodium sulfate, filtered, and concentrated by rotary evaporation to give a pale-yellow oil (8.92 g, 85.0%).

At page 41, lines 4-12, please delete the present paragraph and insert the following:

A mixture of 3,5-dibromopyridine (23.60 g, 100.0 mmol), 4-penten-2-ol (10.8 g, 125.0 mmol), palladium(II) acetate (230 mg, 1.02 mmol), tri-o-tolylphosphine (1.20 g, 3.94 mmol), triethylamine (29.7 mL, 213.45 mmol), and acetonitrile (40 mL) ~~were~~ was heated in a sealed glass tube at 140°C for 14 h. The reaction mixture was cooled to ambient temperature, diluted with water, and extracted with chloroform (3 x 200 mL). The combined chloroform extracts were dried over sodium sulfate and filtered. Removal of solvent by rotary evaporation, followed by column chromatography over silica gel eluting with acetone-chloroform (1:9, v/v) furnished 8.10 g (34.0%) of a pale-yellow oil.

At page 43, lines 3-9, please delete the present paragraph and insert the following:

A mixture of 5-bromo-3-methoxypyridine (4.11 g, 21.86 mmol), 4-penten-2-ol (2.25 g, 26.23 mmol), palladium(II) acetate (49 mg, 0.22 mmol), tri-o-tolylphosphine (266 mg, 0.87 mmol), triethylamine (13.71 mL, 98.37 mmol), and acetonitrile (15 mL) ~~were~~ was heated in a sealed glass tube at 140°C for 14 h. The reaction mixture was cooled to ambient temperature, diluted with water, and extracted with chloroform (3 x 200 mL). The combined chloroform extracts were dried over sodium sulfate, filtered, and concentrated by rotary evaporation to give 3.53 g (70.3%) of a pale-yellow oil.

At page 44, lines 19-27, please delete the present paragraph and insert the following:

Sample No. 8 exhibits an E_{max} of 10% (at a concentration of 100 μM) at muscle-type receptors, indicating that the compound does not induce activation of muscle-type receptors. The sample exhibits an E_{max} of 2% (at a concentration of 100 μM) at ganglionic-type receptors. The compound has the capability to activate human CNS receptors without activating muscle-type and ganglionic-type nicotinic acetylcholine receptors to any significant degree. Thus, there is provided a therapeutic window for utilization in the treatment of CNS disorders. That is, at certain levels the compound shows CNS effects to a significant degree but ~~do~~ does not show undesirable muscle or ganglion effects to any significant degree.